Customer No. 35743

Docket No. 57637/1342

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Von Wronski et al. Confirmation No. 6852

Serial No.: 09/871,974

Filing Date: June 4, 2001

For: COMPOUNDS FOR TARGETING ENDOTHELIAL CELLS, COMPOSITIONS CONTAINING THE SAME AND METHODS FOR THEIR USE

Examiner: Audet, M.

Group Art Unit: 1654

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: 5/25/05

Signature: C. Caggiano

Carrie L. Caggiano

Sir:

DECLARATION OF MATHEW VON WRONSKI, PH.D.

I, Mathew von Wronski, Ph.D., declare as follows:

1. I am a citizen of the United States of America, and currently reside in Moorestown, New Jersey.

2. I received a Bachelor of Arts degree in chemistry in 1982 from Central College, Pella, Iowa and a Bachelor of Science degree in Basic Medical Sciences in 1984 from the University of Southern Alabama, Mobile, Alabama. I received a Ph.D. in Basic Medical Sciences in 1989 from the University of Southern Alabama.

3. For over six years, I have been engaged in the research and development of diagnostic imaging and therapeutic agents, including targeted imaging agents and targeted therapeutics. Since 1998, I have been, and currently am, employed by Bracco Research USA,

305 College Road East, Princeton, New Jersey ("Bracco Research") as a research scientist with duties relating to research and development of diagnostic imaging agents, including labeling compounds and methods.

4. I am also an inventor and/or co-inventor of numerous patent applications owned by Bracco, including various United States, European, and other applications worldwide relating to constructs for diagnostic imaging and therapy, and methods of making the same. I am a co-inventor of U.S. Patent Application No. 09/871,974.

5. I have reviewed the above referenced U.S.S.N. 09/871,974, including the currently pending claims, and am familiar with the subject matter disclosed and claimed therein.

6. I have reviewed the Office Action mailed February 25, 2005 ("Office Action"), and make this declaration in support of the concurrently filed *Response To Office Action*.

A. The Term "TKPPR Analogue"

7. As an initial matter, an analogue as used in the chemical and biochemical fields is a structural derivative of a parent compound that often differs from it by a single element (*The American Heritage Dictionary of the English Language*, 4th Ed. 2000).

8. Over the last five years, I have both conducted searches and reviewed numerous references relating to TKPPR and TKPPR analogues, and have found that references containing TKPPR are comprehensive and cumulative of any references that disclose TKPPR analogues. In other words, I do not recall ever having seen any references that disclose TKPPR analogues which does not also disclose TKPPR itself. This observation is consistent with the well known and well understood scientific principle that TKPPR analogues are derived from TKPPR, and thus, any references which disclose TKPPR analogues will also disclose TKPPR.

B. Enablement

9. I understand that in the Office Action, claims 1, 23-36 and 49 and were rejected for failing to comply with the "enablement" requirement of 35 U.S.C. § 112, ¶ 1 based on the term "TKPPR analogue."

10. I have been informed by the attorneys for U.S.S.N. 09/871,974 ("Applicants' attorneys") that the standard for determining whether the specification meets the enablement requirement of 35 U.S.C. § 112, ¶ 1 is whether the experimentation needed to practice the claimed invention is undue.

11. I have further been informed by Applicants' attorneys that one skilled in the art would be an individual with an undergraduate degree in chemistry or biochemistry and at least two years of graduate or postdoctoral work or work experience in the field of radiodiagnostic or radiotherapeutic applications.

12. The presently claimed invention is directed to compositions comprising a monomer of TKPPR, or a monomer of a TKPPR analogue which specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR, as well as methods of ultrasound imaging comprising administering an ultrasound contrast agent comprising such compositions.

13. As an initial matter, it is my opinion that one of ordinary skill in the art would understand based on the Specification for U.S.S.N. 09/871,974 ("the '974 Specification") how to practice the claimed invention with "a monomer of a TKPPR analogue" without any undue experimentation.

14. Furthermore, I note that the claimed invention recites "a monomer of a TKPPR analogue *that specifically binds to NP-1 cells or cells that express NP-1 with avidity that*

is equal to or greater than TKPPR" and not just any "TKPPR analogue." In other words, this recited limitation is much narrower than a monomer of a "TKPPR analogue." Thus, it is also my opinion that one of ordinary skill in the art based on the '974 Specification would understand how to practice the claimed invention with "a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR" without any undue experimentation.

15. The reasons for my conclusions in the preceding paragraphs are simple. First, in the pharmaceutical, chemical, and biological fields, it is well known and common that one of ordinary skill in the art reviewing a reference which teaches the use of a parent compound would invariably also then understand how to practice the invention with an analogue of the parent compound without undue experimentation. This is because the chemistry of analogues or analogs are well understood and thus, there exists a level of predictability in the art between parent compounds and their analogues. Experimentation, if any is needed, would be routine at most.

16. Next, the '974 Specification itself discloses how to practice the claimed invention with a monomer of TKPPR. The '974 Specification discloses examples of how to practice the claimed invention with a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR (*see, e.g.*, Examples 4 and 14, which discuss GTKPPR). The '974 Specification further teaches. TKPPR analogues that are useful in the present invention have specific characteristics – for example, they include molecules that target the NP-1 VEGF binding receptor with avidity that is greater than or equal to TKPPR ('974 Specification, pages 10-11). Examples of acceptable TKPPR analogues are listed throughout the '974 Specification, *e.g.*, at page 11, lines 18-23. The

'974 Specification lists examples of TKPPR analogues that result from, *e.g.*, amino acid substitutions, "made with synonymous groups" (page 11, lines 3-9). Indeed, the '974 Specification even provides specific amino acids which may be substituted for each of the Thr, Lys, Pro and Arg residues in TKPPR. See Table, page 11. Furthermore, the '974 Specification teaches that TKPPR analogues may be prepared from deletions or insertions of amino acids in the TKPPR sequence or from muteins or of the TKPPR sequence (page 10, lines 20-26) as well as from peptidomimetics or pseudopeptides incorporating changes to the amide bonds of the peptide backbone (page 11, lines 18-19). Thus, the '974 Specification provides ample guidance on practicing the claimed invention, both when A is a monomer of TKPPR and when A is a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR.

17. Armed with this knowledge of how to practice the claimed invention with a monomer of a TKPPR and a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR, one of ordinary skill in the art would clearly understand how to practice the claimed invention with any other monomers of TKPPR analogues that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR. Experimentation, if any is needed, would be routine at most, and certainly would not be undue.

18. Therefore, it is my opinion that one skilled in the art would be able to practice the invention of claims 1, 23-36 and 49 without undue experimentation when A is a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR.

I HEREBY DECLARE that all statements made of my own knowledge are true, and all statements made on information and belief are believed to be true. I make this declaration understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Dated: May 24, 2005

Respectfully submitted,

By: M. A. von Wronski

Mathew von Wronski, Ph.D.